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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,085	03/05/2002	John Ford	28110/35761A	6888

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,085	FORD ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-13 and 16* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/25/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 12-14 and 16 are pending.

2. Applicant's election without traverse of Group 4 (claims 12-14 and 16) drawn to an isolated polypeptide with NDPase activity and a composition comprising said polypeptide filed 12/10/03 is acknowledged.

3. Claims 12-14 and 16 are being acted upon in this Office Action.

4. Applicant should amend the first line of the specification to update the relationship between the instant application and 09/350,836, filed 7/9/99, which is now Pat No. 6,387,645.

5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

6. The references A11-A12 and C131-132 cited on PTO 1449 filed 6/25/02 have been considered but crossed out because USSNs (A11-A12) and International search report (C131-132) are not appropriate for IDS.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 12-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated polypeptide with NDPase activity comprising SEQ ID NO: 3, (2) an isolated polypeptide with NDPase activity comprising the CD39-like protein of SEQ ID NO: 3 wherein the polypeptide consists of at least one amino acid substitution selected from the group consisting of D at position 168 to T, S at position 170 to T, L at position 175 to F of SEQ ID NO: 3 and wherein the polypeptide has increase ADPase activity, (3) The said isolated polypeptide having the amino acid sequence set forth in SEQ ID NO: 7 and (4) a composition

comprising said polypeptide and a carrier for inhibiting platelet aggregation in vitro and screening assays, **does not** reasonably provide enablement for (1) *any* isolated polypeptide with NDPase activity comprising *any* amino acid sequence having at least "about 80% sequence identity" to SEQ ID NO: 3, (2) *any* isolated polypeptide with NDPase activity comprising the CD39-like protein coding sequence of SEQ ID NO: 3 wherein the polypeptide comprises at least one amino acid substitution selected from the group consisting of: D168 → T, S170 → Q and L175 →F, (3) *any* isolated polypeptide with NDPase activity comprising *any* amino acid sequence having at least "about 80% sequence identity" to SEQ ID NO: 3 wherein the polypeptide comprises at least one amino acid substitution selected from the group consisting of: D168 → T, S170 → Q and L175 →F, and (4) *any* composition comprising any isolated polypeptide mentioned above and a pharmaceutically acceptable carrier for treating any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only an isolated polypeptide with NDPase activity comprising SEQ ID NO: 3, an isolated polypeptide with NDPase activity comprising the CD39-like protein of SEQ ID NO: 3 wherein the polypeptide consists of at least one amino acid substitution selected from the group consisting of D at position 168 to T, S at position 170 to T, L at position 175 to F of SEQ ID NO: 3 and wherein the polypeptide has increase ADPase activity, (3) The said isolated polypeptide having the amino acid sequence set forth in SEQ ID NO: 7 and (4) a composition comprising said polypeptide and a carrier for inhibiting platelet aggregation in vitro and screening assays.

The specification does not teach how to make and use *any* polypeptide *any* isolated polypeptide with NDPase activity comprising *any* amino acid sequence having at least "about 80% sequence identity" to SEQ ID NO: 3 because there is insufficient guidance as to the structure

without the specific amino acid sequence of any amino acid sequence having at least about 80% identity to SEQ ID NO: 3. It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even a single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Mikayama *et al.*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that amino acid sequence determines the function of the polypeptide or protein. However, the predictability of which changes can be tolerated in an amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance such as which amino acids within the full-length polypeptide are tolerant of modification and which amino acid residues are conserved or less tolerant to modification in which the product's structure relates to its functional usefulness. In fact, the specification discloses that mutations in ACR I and II eliminate activity, whereas the mutations in ACR III increase activity six-fold over wild type (Figure 7). The use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Because applicants have not disclosed the specific condition used to score sequence identity while using any computer program mentioned above, it is unpredictable to determine which amino acid sequences will have at least about 90% identity to the claimed sequence and still retains the activities. Thus it would require undue experimentation for one of skill in the art to identify polypeptide that merely has 80% identical to the claimed sequence of SEQ ID NO: 3 but also has functional activity. Further, the term "about" expands the lower and upper limits of the percentage of identity. Since the polypeptide is less than 80% identical SEQ ID NO: 3, there is at least 10% or more differences.

Attwood *et al.* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document).

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). A polypeptide having at least about 80% identity to SEQ ID NO: 3 mean at least about 90 amino acid differences.

It is unpredictable which undisclosed polypeptide having at least about 90 amino acid differences would maintain its structure and biological function such as NDPase activity, in turn, would be useful for treating any disease. Further, there is no in vivo working example demonstrating any isolated polypeptide with NDPase activity is effective for treating indefinite number of disease.

As to claim 13, because the structure of said polypeptide having at least about 80% identity to SEQ ID NO: 3 is not enabled, it follows that any amino acid substitution such as D168 → T, S170 → Q and L175 →F is not enabled.

Grinthal *et al* teach that substitution of His59 converts CD39 apyrase into an ADPase in a quaternary structure dependent manner (See entire document, abstract, in particular). Even if the specific amino acid substitutions as set forth in claim 3 are within the polypeptide of SEQ ID NO: 3, there is insufficient guidance as to the function of the modified polypeptide, in turn, useful for treating any disease. Since the polypeptide is not enabled, it follows that the composition comprising said polypeptide is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 12-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* isolated polypeptide with NDPase activity comprising *any* amino acid sequence having at least "about 80% sequence identity" to SEQ ID NO: 3, (2) *any* isolated polypeptide with NDPase activity comprising the CD39-like protein coding sequence of SEQ ID NO: 3 wherein the polypeptide comprises at least one amino acid substitution selected from the group consisting of: D168 → T, S170 → Q and L175 →F, (3) *any* isolated polypeptide with NDPase activity comprising *any* amino acid sequence having at least "about 80% sequence identity" to SEQ ID NO: 3 wherein the polypeptide comprises at least one amino acid substitution selected from the group consisting of: D168 → T, S170 → Q and L175 →F, and (4) *any* composition comprising any isolated polypeptide mentioned above and a pharmaceutically acceptable carrier for treating any disease.

The specification discloses only an isolated polypeptide with NDPase activity comprising SEQ ID NO: 3, an isolated polypeptide with NDPase activity comprising the CD39-like protein of SEQ ID NO: 3 wherein the polypeptide consists of at least one amino acid substitution selected from the group consisting of D at position 168 to T, S at position 170 to T, L at position 175 to F of SEQ ID NO: 3 and wherein the polypeptide has increase ADPase activity, (3) The said isolated polypeptide having the amino acid sequence set forth in SEQ ID NO: 7 and (4) a composition comprising said polypeptide and a carrier for inhibiting platelet aggregation in vitro and screening assays.

Other than the specific polypeptide with NDPase activity for inhibiting platelet aggregation or screening assay, there is inadequate written description about the structure such as the amino acids associated with function of any polypeptide having at least about 80% identity to SEQ ID NO: 3 (428 amino acids) because 80% identity means at least 20% difference, which is equivalent to at least about 90 amino acids differences. The term "about" expands the lower and upper limits of the 20% difference. There is insufficient written description about the structure (amino acid sequence) of any polypeptide having at least about 80% identity to SEQ ID NO: 3, much less having NDPase activity. Further, given that the structure of any polypeptide having at least about 80% identity to SEQ ID NO: 3 is not adequately described, the amino acid substitution such as the ones recited in claim 13 and the corresponding function of said

polypeptide are not adequately described. Even if the amino acid substitution is limited to within SEQ ID NO: 3, the function of modified polypeptide is not adequately described. Since the polypeptides mentioned above are not adequately described, the composition comprising said polypeptide for treating any disease is not adequately described.

The specification discloses only two polypeptide comprising SEQ ID NO: 3 and 7 (modified) having NDPase activity. Given the lack of a written description of *any* additional representative species of polypeptide having NDPase activity, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 12-13 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "at least about" in claim 12 and 16 is ambiguous and indefinite because the minimum sequence identity is not clear.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 12 is rejected under 35 U.S.C. 102(a) as being anticipated by Chadwick *et al* (Genomics 50: 357-67, June 1998; PTO 1449).

Chadwick *et al* teach an isolated CD39L4 polypeptide that is 100% identical to the claimed polypeptide of SEQ ID NO: 3, which is at least about 80% identical (See page 162,

column 2, Figure 1, in particular). The reference polypeptide inherently has NDPase activity since the reference sequence is 100% identical to the claimed sequence. Chadwick *et al* further teach various CD39 polypeptides such as CD39L2, potapyrase, dNTPase and yGDPase which are at least about 80% identical to the claimed SEQ ID NO: 3 (See Figure 1, CD39L2, Figure 4, page 365, in particular). The term comprising is open-ended. It expands the claimed polypeptide fragment to include additional amino acid at either or both ends to read on the reference polypeptide. Thus, the reference teachings anticipate the claimed invention.

14. Claim 12 is rejected under 35 U.S.C. 102(a) as being anticipated by Chadwick *et al* (Mammalian Genome 9: 162-164, Feb 1998; PTO 1449).

Chadwick *et al* teach an isolated mouse NTPase polypeptide that is 88.6% identical to the claimed polypeptide of SEQ ID NO: 3, which is at least about 80% identical (See page 359, Figure 1, in particular). The reference polypeptide inherently has NDPase activity.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chadwick *et al* (Genomics 50: 357-67, June 1998; PTO 1449) or Chadwick *et al* (Mammalian Genome 9: 162-164, Feb 1998; PTO 1449) each in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 287) or Gennaro *et al* in Remington's Pharmaceutical Sciences, eighteenth edition, 1990, pages 1300-1329; PTO 892).

The teachings of both Chadwick *et al* have been discussed supra.

The claimed invention differs from the teachings of the references only by the recitation of a pharmaceutically acceptable carrier.

Harlow et al teach a pharmaceutical acceptable carrier such as PBS and it is conventional to store polypeptide in phosphate buffered saline (PBS) or similar isotonic solution (See page 287, in particular).

Gennaro *et al* teach various pharmaceutical acceptable carrier such as purified water, dextrin, sodium carbonate, (See page 1301, page 1321, in particular). Gennaro *et al* teach that pharmaceutical carrier and vehicle are indifferent substances which are useful as solvents for active medicinals and primary importance for diluting and flavoring drugs. Gennaro *et al* teach that the best diluting agent is usually the best solvent for the drug (See page 1300, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to store the polypeptide as taught by both Chadwick et al in a pharmaceutically acceptable carrier as taught by Harlow et al or Gennaro et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow et al teach that it is conventional to store polypeptide in phosphate buffered saline (PBS) or similar isotonic solution (See page 287, in particular). Gennaro et al teach that pharmaceutical carrier and vehicle are solvents for active medicinals and primary importance for diluting and flavoring drugs and the best diluting agent is usually the best solvent for the drug (See page 1300, in particular).

18. Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196. .

20. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The IFW official Fax number is (703) 872-9306.

Phuong N. Huynh, Ph.D.
Patent Examiner
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February 9, 2004

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